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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,618	12/22/2004	Michael F. Holick	2317.0430001/RWE	8983

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EXAMINER

WESTERBERG, NISSA M

ART UNIT	PAPER NUMBER
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4173

MAIL DATE	DELIVERY MODE
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12/20/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/518,618	Applicant(s) HOLICK ET AL.	
	Examiner NISSA M. WESTERBERG	Art Unit 4173	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 - 11 is/are pending in the application.
- 4a) Of the above claim(s) 3 - 7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2 and 8 - 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

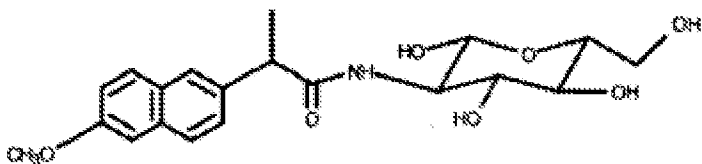
Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>3/7/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of the second naproxen-glucosamine conjugate in paragraph [0017],



in the reply filed on November 16, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

The search was not expanded beyond the elected species

Status of Claims

Claims 1 – 11 are pending. Claims 3 – 7 are withdrawn as being drawn to the non-elected invention. Claims 1, 2 and 8 – 11 are currently under examination.

Claim Rejections - 35 USC § 112 1st Paragraph

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2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of pain, fever, condition characterized by an inflammatory process, does not reasonably provide enablement for the prevention of pain, fever, condition characterized by an inflammatory process and cancer and the treatment of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The disclosure and claims of the application have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2nd 1400 (Fed. Cir. 1988) as to undue experimentation

The factors include:

1. The nature of the invention;
2. The breadth of the claims;
3. The predictability or unpredictability of the art;
4. The amount of direction or guidance presented;
5. The presence or absence of working examples
6. The quantity of experimentation necessary;
7. The state of the prior art; and
8. The relative skill of those skilled in the art.

Each factor is address below on the basis of comparison of the disclosure, the claims and the state of the art in the assessment of undue experimentation.

1. The nature of the invention: a compound consisting of a non-steroidal anti-inflammatory drug (NSAID) is linked to a sugar, but the compound is not an indolyl acid amide.

2. The breadth of the claims: Compounds meeting aforementioned limitation are included, as well as a pharmaceutical composition comprising the compound and a pharmaceutically acceptable carrier. Methods to treat and prevent pain, fever, condition characterized by an inflammatory process or cancer using the NSAID linked sugar compound are also claimed.

3. The amount of direction or guidance presented, the presence or absence of working examples: Structures and synthesis procedures for various NSAID compounds linked to a sugar are put forth. No results regarding characteristics of the synthesized compounds are presented.

4. The predictability or unpredictability of the art, the quantity of experimentation necessary, state of the prior art and the relative skill of those skilled in the art: The relative skill of those skilled in the art is high. NSAIDs are a class of drugs that are

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known to be anti-inflammatory, antipyretic (anti-fever) and analgesic (pain reliever) agents (p 692 col 2, last paragraph of "NSAIDs: Nonsteroidal Antiinflammatory Drugs" in Goodman and Gilman, 14th Edition, 2001, p 687 – 696). NSAIDs are a heterogeneous group of compounds (p 687, col 1, 1st paragraph) which have varying levels of selectivity (Table 27-1, p 691) and side effects (table 27-2, p 694). For example, the common NSAID acetaminophen does not possess anti-inflammatory activity but does have antipyretic and analgesic activity (p 692, col 2, last line – p p 693, col 1, ln 2). There is evidence that some NSAIDs, such as sulindac sulfide, may be useful in the treatment of colon cancer (p 693, col 2, last paragraph).

The term "cancer" encompasses a large number of types of cancer (e.g., lung, breast and skin). Many additional types of cancer are present within each type of cancer. For example, the Merck Manual of Medical Information (Second Home Edition, last full review/revision February 2003) entry for breast cancer indicates that even within this one breast cancer, the cells of different tumors are heterogeneous (p 5, "Characteristics") with different receptors being expressed and different prognoses for the disease based on the particular characteristics of those tumors.

The claims contain language regarding both the treatment and prevention of the listed disorders. "Prevent" (dictionary.com entry accessed 11/28/2007) is defined to mean that something is stopped from being in a certain state or made impossible (p 3). There is no evidence to indicate that administration of the compound will result in the animal never developing pain, a fever, a condition characterized by inflammation or cancer.

Therefore, Applicant is not enabled for the prevention of any of the listed disorders. Applicant is also not enabled for the treatment of cancers with NSAIDs linked to a sugar. Applicant is enabled for methods of treatment for pain, fever and inflammation with NSAIDs linked to a sugar.

Claim Rejections - 35 USC § 112 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claims recites "reduced and/or fewer side effects". As claimed, to determine if the method has reduced and/or fewer side effects, the method comprises a step in which "an effective amount of a compound consisting of an NSAID linked to a sugar" is administered and the side effects are compared to one in which "the corresponding underivatized NSAID is administered to the animal." P 20, paragraph [0047] of the specification recites that the comparison "may be measured by administering the compounds of the invention and underivatized NSAIDS in equimolar amounts." However, that limitation is not present in the claims and the amount of underivatized NSAID administered in the method as claimed to establish the benchmark level of side effects cannot be determined.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

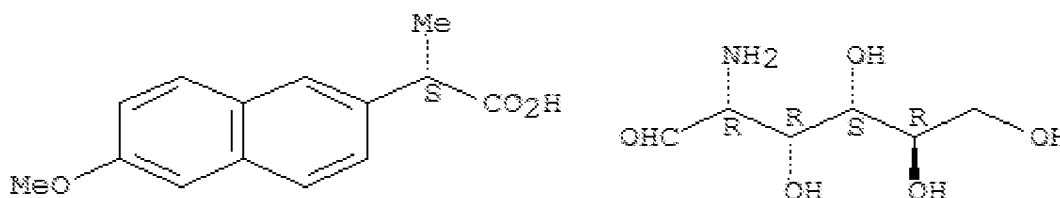
8. Claims 1, 2, and 8 – 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cramer et al. (WO 97/04808).

Cramer et al. discloses compositions comprising an analgesic agent and certain antihistamines for the improved treatment, management or mitigation of cold, cold-like, allergy, sinus and/or flu symptoms (p 1, ln 11 – 15). NSAIDs are used to combat inflammation and pain (p 2, ln 12 – 15). One example of an NSAID is naproxen (p 2, ln 17), which is a propionic derivative (see chemical structure on the next page of this

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Action and claims 3 and 4 on page 13 of Cramer et al.). Pharmaceutically acceptable salts can be prepared using glucosamine (p 3, ln 33 – p 4, ln 6). Claim 6 (p 14) regards a composition in which a propionic acid derivative is present as the amino acid salt and glucosamine is exemplified as a compound that can be used to form such a salt.

In a salt, the hydrogen of an acid is replaced by a metal or equivalent like NH_4^+ (definition of salt, Hawley's Condensed Chemical Dictionary, 14th Edition, 2002). Shown below are the structures of naproxen (left) and glucosamine (right):



The $-\text{NH}_2$ group of the glucosamine can be protonated to form a $-\text{NH}_3^+$ group, which replaces the hydrogen atom of the $-\text{CO}_2\text{H}$ group in the naproxen to form a salt. In the glucosamine salt of naproxen, the NSAID naproxen is linked to a sugar, glucosamine, and therefore meets the limitations of the claim 1.

The compositions are also taught as being useful in methods of treatment of flu, which generally includes fever (p 1, ln 34 – 36) and for the treatment of pain and inflammation (p 2, ln 12 – 18). These composition can be in various dosage forms and these dosage forms can contain pharmaceutically acceptable carriers (p 6, ln 18 - p 7, 8).

Therefore, the teachings of Cramer et al. make obvious the claims of the instant invention in which naproxen is linked to glucosamine.

Conclusion

Claims 1, 2 and 8 – 11 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571) 270-3532. The examiner can normally be reached on M - F, 7:30 a.m. - 5 p.m. ET. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718 or Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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NMW

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614